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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/992,235	LEDERMAN ET AL.	
	Examiner	Art Unit	
	LESLIE A. ROYDS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,25-28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,28 and 30-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8, 25-28 and 30-31 are presented for examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2009 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 1-8, 25-28 and 30-31 are pending. Claims 25-27 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 1-8, 28 and 30-31 remain under examination. Claim 29 is cancelled. Claims 30-31 are amended.

Applicant's arguments, filed February 27, 2009, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Error Noted in Claim Listing Dated February 27, 2009

Applicant has indicated the status of instant claim 28 as "Withdrawn" in the claim listing filed with the request for continued examination (RCE) dated February 27, 2009. However, as noted in the final rejection dated December 4, 2008, instant claim 28 has been examined and is not properly withdrawn from consideration at this time. Accordingly, claim 28 is under examination, despite the incorrect status identifier provided in the claim listing of February 27, 2009, and is herein examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 28 and 30-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Salvesen et al. ("NMR and ORD Determination of the Configuration of the N-Cyanobenzylamphetamine (AN 1)", *Aezneim-Forsch. (Drug Res.)*, 1974; 24(2):137-140), in light of STN Registry File No. 17590-01-1 ("Amphetaminil", 2008) and Stedman's Medical Dictionary (Twenty-Second Edition, 1972; p.377), each cited to show facts, in view of Remington's Pharmaceutical Sciences (Sixteenth Edition, 1980; p.42-425), each already of record, for the reasons of record set forth at p.10-18 of the previous Office Action dated December 4, 2008, of which said reasons are herein incorporated by reference.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Applicant has shown that the claimed isomeric configuration is more effective as a stimulant and has fewer movement-related side effects as compared to the racemate. Applicant submits that this simultaneous increase in activity and decrease in

toxicity is surprisingly and unexpectedly advantageous and, thus, constitutes an unexpected result. Applicant alleges this result was not predictable and asserts that the artisan would have expected the opposite effect, i.e., that a compound's toxicity would increase with its increased therapeutic effect. Still further, Applicant states that the instant claims are directed to a single isomer and there is no teaching, suggestion or motivation in Salvesen et al. to make the purified amphetaminil isomer as instantly claimed.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant alleges that the present invention is non-obvious over the prior art because the single amphetaminil isomer instantly claimed [i.e., (R,R'),(R,S')-amphetaminil] demonstrated a simultaneous increase in stimulant activity and a decrease in toxicity (specifically, movement-related side effects) and relies upon the data presented in the instant specification as evidence of unexpected results probative of nonobviousness. While such results have been carefully and closely considered, it remains that the results fail to be commensurate in scope with the presently claimed subject matter because: (1) the compound used in Example 4 upon which Applicant relies was the sulfate salt of (R,R'),(R,S')-amphetaminil, whereas the presently claimed subject matter is directed to the use of (R,R'),(R,S')-amphetaminil sulfate *or another pharmaceutically acceptable salt thereof*; (2) the compounds of the invention appear to have been administered in a 100% DMSO vehicle [see p.27 of the instant specification at Example 4, which states, "Compounds were administered at the doses: 0.1, 1 and 10 mg/kg s.c. in 100% DMSO (vehicle)."], whereas the presently claimed subject matter is directed to the use of at least one pharmaceutically acceptable carrier, diluent, excipient or additive *of any type*; (3) the (R,R'),(R,S')-amphetaminil sulfate compound was administered in three specific dosage amounts (i.e., 0.1, 1 and 10 mg/kg) *subcutaneously*, whereas the presently claimed subject matter in its broadest embodiment is directed to the use of *any* therapeutically effective amount and *any* administrable form (i.e., oral, topical, subcutaneous, etc.); and (4) the highest concentration of (R,R'),(R,S')-amphetaminil sulfate studied (i.e., 10 mg/kg), in fact, demonstrated an *increase* in movement-related side effects as

evidenced by Figures 3B and 7B (which are discussed at p.31-32) and, thus, failed to demonstrate an unexpected decrease in movement related side effects as observed with racemic amphetaminil.

Applicant's attention is directed to Example 4 at p.31, which states: "(R,R'),(R,S')-amphetaminil (Figure 3) increased locomotor activity only at the highest dose of 10 mg/kg (Fig.3A-B; significant effect of treatment ($p<0.001$), two-way ANOVA)." A comparison of the cumulative locomotor activity observed over 300 min for both (R,R'),(R,S')-amphetaminil (Figure 3B) and for racemic amphetaminil (Figure 4B) shows that, for both (R,R'),(R,S')-amphetaminil and racemic amphetaminil, a clear increase in locomotor activity was observed when 10 mg/kg s.c. was administered. Notably, also, a comparison of 0.1 mg/kg s.c. (R,R'),(R,S')-amphetaminil and 0.1 mg/kg s.c. racemic amphetaminil as presented in Figures 3B and 4B demonstrates that 0.1 mg/kg s.c. (R,R'),(R,S')-amphetaminil showed greater locomotor activity than that seen with the racemate. Accordingly, the allegedly unexpected effect of decreased locomotor activity of the instantly claimed (R,R'),(R,S')-amphetaminil sulfate isomer appears to only have been demonstrated at the 1 mg/kg s.c. amount when compared to the locomotor activity observed with equivalent amounts of the racemate.

Applicant's attention is also directed to Example 4 at p.32, which states: "(R,R'),(R,S')-amphetaminil (Figure 7) tended to increase stereotypy at 10 mg/kg (Fig.7A-C) although differences did not reach statistical significance ($p>0.05$, Kruskall-Wallis)." A comparison of the total stereotypy score observed over 300 min for both (R,R'),(R,S')-amphetaminil (Figure 7B) and for racemic amphetaminil (Figure 8B) shows that, for both (R,R'),(R,S')-amphetaminil and racemic amphetaminil, a clear increase in total stereotypy score was observed when 10 mg/kg s.c. was administered. Notably, also, a comparison of 0.1 mg/kg s.c. (R,R'),(R,S')-amphetaminil and 0.1 mg/kg s.c. racemic amphetaminil as presented in Figures 7B and 8B demonstrates an apparently equivalent total stereotypy score for both the single isomer instantly claimed and that of the racemate. Accordingly, the allegedly unexpected effect of decreased stereotypy of the instantly claimed (R,R'),(R,S')-amphetaminil sulfate isomer appears to only have been

demonstrated at the 1 mg/kg s.c. amount when compared to the total stereotypy observed with equivalent amounts of the racemate.

Though it is noted that the proffered data does appear to demonstrate an unexpected decrease in movement-related side effects at least for the use of (R,R'),(R,S')-amphetaminil sulfate in 100% DMSO in an amount of 1 mg/kg to be administered subcutaneously that would not necessarily have been expected or predicted from the prior art, it remains that the proffered results do not provide a basis for concluding that the *full scope* of the instantly claimed subject matter would not have been obvious because the results that support the decrease in movement-related side effects while preserving stimulant activity are (1) limited solely to (R,R'),(R,S')-amphetaminil sulfate, (2) limited to 1 mg/kg of (R,R'),(R,S')-amphetaminil sulfate to be administered subcutaneously and (3) limited to a 100% DMSO vehicle, while the claims subject to this rejection encompass (1) (R,R'),(R,S')-amphetaminil (instant claim 28) or (R,R'),(R,S')-amphetaminil sulfate *or any other pharmaceutically acceptable salt thereof* (instant claims 1 or 30), (2) *any* therapeutically effective amount (instant claim 1) or effective amount (instant claim 30) of the claimed isomer, and (3) at least one of *any* type of pharmaceutically acceptable carrier, diluent, excipient or additive (instant claims 1 or 30). Further, it has not been argued or demonstrated on the record that the results obtained with the exemplified composition(s) would have been exemplary of the same or substantially equivalent results that would have been expected to occur over the entire scope of the claimed subject matter.

In this regard, MPEP §2144.08(II)(B) is relied upon and reads, in-part: "When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the Applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of

obviousness. Id. For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a *prima facie* case of obviousness if a skilled artisan 'could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof.' *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (**Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.**) But see, *In re Grasselli*, 713 F.2d at 743, 218 USPQ at 778 (Evidence of superior properties for sodium containing composition insufficient to establish the non-obviousness of broad claims for a catalyst with 'an alkali metal' where it was well known in the catalyst art that different alkali metals were not interchangeable and Applicant had shown unexpected results only for sodium containing materials); *In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978) (Evidence of superior properties in one species insufficient to establish the nonobviousness of a subgenus containing hundreds of compounds); *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (one test not sufficient where there was no adequate basis for concluding the other claimed compounds would behave the same way)." (emphasis added)

Here, just as a single point in space fails to define a line, even though the results shown with a particular concentration (i.e., 1 mg/kg s.c.) of the sulfate salt of (R,R'),(R,S')-amphetaminil in a 100% DMSO vehicle appear to demonstrate an unexpected decrease in movement-related side effects when compared to racemic amphetaminil while preserving the stimulant effect of the compound that was both unexpected and unpredictable from the prior art, the results demonstrated for this particular composition would be insufficient to establish the non-obviousness of the entirety of the presently claimed combinations (i.e., *any* pharmaceutically acceptable salt of (R,R'),(R,S')-amphetaminil, *any* effective or therapeutically effective amount of (R,R'),(R,S')-amphetaminil sulfate or *any* pharmaceutically acceptable salt thereof, or the use of at least one of *any* type of pharmaceutically acceptable carrier, diluent, excipient

or additive) absent any concrete evidence or scientifically sound reasoning as to why these other embodiments would have been reasonably expected to demonstrate the same or at least a substantially equivalent unexpected effect, particularly with using different formulations of the active compound as different pharmaceutically acceptable salts, in different amounts, carriers, etc.

Accordingly, while Applicant's data provided in the instant specification has been fully and carefully considered, it remains that Applicant has not provided sufficient evidence and/or explanation to support the allegation that an unexpected effect over the entire scope of the claimed subject matter has been demonstrated. Furthermore, even though an apparently unexpected effect has been demonstrated for the particular composition provided in Example 4 of the instant specification wherein the isomer was present in an amount of 1 mg/kg, Applicant has not provided any objective evidence, scientific reasoning or persuasive argument on the record to provide an adequate basis for concluding that this particular combination demonstrated in Example 4 was somehow probative of the same (or at least substantially equivalent) unexpected effect over the entire scope of the claimed invention. In short, the evidence is, respectfully, insufficient to be supportive of nonobviousness on the grounds of an unexpected effect and not commensurate in scope with the claimed subject matter.

Applicant is reminded that should he rely upon unexpected results to patentably distinguish over the prior art, the present claims must be limited to the embodiment(s) which is (are), in fact, unexpected. Note also that Applicant is burdened with the responsibility of explaining why the evidence provided to support secondary considerations is probative of non-obviousness beyond what data is explicitly provided as unexpected. Please see MPEP §716.02(b)[R-2], particularly Section (II), which states, "[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." *Ex parte Ishizaka*, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992). In the instant case, though the instant data was provided in the instant specification and not a declaration, the burden is nonetheless on Applicant to explain the data provided as evidence of non-obviousness of the claimed subject matter.

Moreover, Applicant is reminded that, "The submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987)." In view of this, and further in view of the fact that the provided evidence fails to be commensurate in scope with the claimed subject matter for the reasons *supra*, the totality of the evidence of nonobviousness fails to outweigh the evidence of obviousness as set forth *supra* when all of the evidence is considered. Accordingly, the rejection is properly maintained.

Lastly, in response to Applicant's argument that there is no teaching, suggestion or motivation in Salvesen et al. to make the purified amphetaminil isomer as instantly claimed, the Examiner defers to the reasons and motivation discussed at p.12 of the previous Office Action dated December 4, 2008. Specifically, though it is noted that Salvesen et al. teaches a formulation containing a racemic mixture of the isomers of N-cyanobenzylamphetamine (i.e., amphetaminil) and fails to *expressly* teach (R,R'),(R,S')-amphetaminil substantially free of (S,R'),(S,S')-amphetaminil, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to modify the stereoisomeric mixture of the compound N-cyanobenzylamphetamine (i.e., amphetaminil) (col.2, para.6, p.138) as disclosed by Salvesen et al., to contain the isomeric configuration with the greatest activity in greater quantity (or as the sole isomer) over the other isomers because isomers within a racemic mixture are reasonably expected to have differing activities such that particular isomers are generally expected to be more active than others due to the fact that living systems are chiral and, thus, preferentially process certain stereochemical configurations over others. In other words, optically active isomer isolation from a racemic mixture would have been *prima facie* obvious to one of skill in the art at the time of the invention due to the reasonable expectation of greater activity from one isomer over the other. Motivation to isolate the most active isomeric configurations from a disclosed mixture flows logically from the desirability of producing a pharmaceutical composition that will produce an optimal therapeutic effect. Please reference *In re Anthony*, 162 USPQ 594, and *In re Adamson*, 125 USPQ 233. Accordingly, such reasoning as provided

supra and at p.12 of the previous Office Action forecloses the argument that no teaching, suggestion or motivation to make the purified amphetaminil isomer instantly claimed was provided.

For these reasons *supra*, and those previously made of record at p.10-18 of the Office Action dated December 4, 2008, rejection of claims 1-8, 28 and 30-31 is proper.

Conclusion

Rejection of claims 1-8, 28 and 30-31 is proper.

Claims 25-27 remain **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the instant application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE A. ROYDS whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

April 6, 2009